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(71)Applicant : GREEN CROSS CORP:THE

(72)Inventor : NISHIZAWA HIROYUKI

(54) AGENT FOR PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

(57)Abstract:

PURPOSE: To obtain an agent for the prevention and treatment of Alzheimer's disease caused by the lowering of intracranial acetylcholine content by using a medium-chain fatty acid triglyceride containing 8-10C fatty acid as a main component.

CONSTITUTION: A medium-chain fatty acid triglyceride containing 8-10C fatty acid such as caprylic acid and capric acid as the constituent fatty acid is used as a main component of the objective agent for the prevention and treatment of Alzheimer's disease. The constituent free fatty acid of the agent passes through the blood-brain barrier into the cerebral spinal fluid and is metabolized in the brain cell to acetyl CoA. Excess acetyl CoA forms acetylcholine together with choline. The amount of the active component in the agent for prevention and treatment of Alzheimer's disease is preferably 5-15wt.%. The agent for the prevention and treatment of Alzheimer's disease is administered e.g. in the form of a fat emulsion. The emulsion is prepared from the above active component, an emulsifier such as phospholipid, water and arbitrary other additive components.

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* NOTICES *

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2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the drugs for prevention of the Alzheimer disease resulting from the fall of the acetylcholine content within a brain, and/or a therapy in detail about an Alzheimer disease prevention therapy agent.
[0002]
[Description of the Prior Art] In the patient of the Alzheimer disease which is one of the senile dementia, generally it is known that the fall of the acetylcholine content within a brain will be accepted, and it has been the important index of drug development to this disease.
[0003] Or the drugs used now or the drugs currently developed will not be because composition of the acetylcholine of supplying in a brain the choline which is the enzyme which compounds acetylcholine, the enzyme which controls decomposition of acetylcholine, or the precursor of acetylcholine is stimulated, they is because a receptor is stimulated with the agonist of a muscarine nature acetylcholine receptor.
[0004]
[Problem(s) to be Solved by the Invention] The conventional drugs of the purpose of this invention are that the action mechanism offers fundamentally different prevention and/or the fundamentally different therapy agent of an Alzheimer disease.
[0005]
[Means for Solving the Problem] In order to attain the above-mentioned purpose, as a result of repeating research wholeheartedly, the configuration free fatty acid of the medium-chain-fatty-acid triglyceride (henceforth "MCT") which uses the fatty acid of carbon numbers 8-10 as a configuration fatty acid passes the blood brain barrier, and shifts to cerebrospinal fluid, and this invention persons are metabolized by even acetyl CoA in a brain cell, and came to complete a header and this invention for acetyl CoA for an excess generating acetylcholine with a choline.
[0006] This invention is an Alzheimer disease prevention therapy agent which is completed based on this new knowledge and uses as a principal component MCT whose configuration fatty acid is a fatty acid of carbon numbers 8-10.
[0007] As MCT in this invention, the triglyceride which consists of saturated fatty acid of carbon numbers 8-10, for example, a caprylic acid, and a capric acid is used. When the configuration fatty acids of MCT are a caprylic acid and a capric acid, in order to reduce the toxicity of MCT, as for the ratio of a caprylic acid and a capric acid, 8:2-4:6 are desirable. MCT consists only of MCT which uses the fatty acid of carbon numbers 8-10 as a configuration fatty acid substantially in this invention. MCT which uses fatty acids other than a carbon number 8 - 10 as a configuration fatty acid to it being substantial here means that you may contain in the amount of extent which does not spoil the purpose of this invention.
[0008] MCT in this invention is manufactured by the approach of the very thing known, for example, is obtained by proper means, such as fractionation of fats and oils with high ester interchange using the

composition from glycerol, partial esterification, and an enzyme or content. For example, it can obtain by re-ESUERU-ization with the fractionation of a fatty acid and glycerol by hydrolysis of cacao butter or a palm fat, and distillation. Moreover, they may be extracted from the Cuphea kind containing 80 - 90% of C10 fatty acid. These triglyceride may not necessarily be high grades and what was contained more than 95% (weight) preferably is suitable for it for example, more than 90% (weight) as a principal component.

[0009] The Alzheimer disease prevention therapy agent of this invention contains MCT five to 15% of the weight preferably one to 50% of the weight, and the administration dosage forms, such as a solid gestalt, powder gestalt, liquefied gestalt, and emulsification gestalt, are not limited at all. That is, a medicine may be prescribed for the patient by parenterals (for example, intubation administration to intravenous administration, the stomach, the duodenum, or jejunum etc.), such as taking orally or injection.

[0010] Lipid microsphere is mentioned as 1 administration dosage forms of the Alzheimer disease prevention therapy agent of this invention. This lipid microsphere is prepared by the conventional method from Above MCT, an emulsifier, water, and a proper addition component.

[0011] What is necessary is to mention phospholipid (yolk phospholipid, soybean phosphatide, etc.), a non-ion system surfactant, etc., and to just be refined by medical application as an emulsifier.

[0012] As phospholipid, purification phospholipid, such as yolk lecithin and a soybean lecithin, is suitable, and it can prepare by the fractionation method by the organic solvent of a conventional method. It mainly consists of phosphatidylcholine and phosphatidylethanolamine and phosphatidylinositol, phosphatidylserine, sphingomyelin, etc. are contained as phospholipid other than this.

[0013] What does not contain phosphatidylethanolamine may be used as phospholipid. After this thing performs organic solvent fractionation with a conventional method, inorganic absorbents, such as silica gel or an alumina, can refine phospholipid, such as the usually available yolk and an soybean. The phospholipid obtained in this way may mainly consist of phosphatidylcholine, and may contain phosphatidylinositol, phosphatidylserine, and sphingomyelin as phospholipid other than this. Furthermore, the phosphatidylcholine itself may be used.

[0014] The water to be used changes with administration gestalten and the thing (for example, purified water) suitable for the things (for example, distilled water for injection, purified water for injection, etc.) or the object for taking orally suitable for intravenous injection is used.

[0015] As a content of each component of lipid microsphere, an oil component (MCT) is 5 - 15% (w/v) preferably, and is the oil component 100 1 to 50% (w/v), for example. They are emulsifiers 1-500 to the section. The section (preferably ten to 50 section) and the thing which consists of water of optimum dose are illustrated.

[0016] in addition, the need -- responding -- further -- an emulsification adjuvant -- [-- for example, the carbon numbers 6-22 of the amount to 0.3 % (w/v) -- desirable --], such as a fatty acid of carbon numbers 12-20, or its salt permitted in pharmacology, and a stabilizing agent -- [-- for example below 0.5 % (w/v) -- desirable -- the cholesterol of the amount below 0.1 % (w/v), or below 5% (w/v) -- desirable --], such as phosphatidic acid of the amount below 1% (w/v), and a high polymer -- [-- for example Preferably 0.1 to 5% (w/v) 0.5 - 1% (w/v) of albumin,], such as a dextran, a vinyl polymerization object, a nonionic surfactant, gelatin, and hydroxyethyl starch, isotonizing agents (for example, a glycerol, grape sugar, etc.), perfume, etc. can also be added.

[0017] All can be used for it if addition in drugs is possible for the fatty acid of the carbon numbers 6-22 as an emulsification adjuvant. Although any of the shape of a straight chain and the letter of branching are sufficient as this fatty acid, it is desirable to use straight chain-like stearin acid, oleic acid, linolic acid, a palmitic acid, a linolenic acid, a myristic acid, etc. As these salts, the salt (for example, sodium salt, potassium salt, etc.) accepted physiologically, for example, alkali-metal salts, alkaline-earth-metal salts (for example, a calcium salt, magnesium salt, etc.), etc. can be used.

[0018] Furthermore, fatty amine may be used as an emulsification adjuvant. Specifically, the thing of carbon numbers 2-22 is illustrated. If addition in drugs is possible for this fatty amine, it can use all. Although any of the shape of a straight chain and the letter of branching are sufficient as this fatty

amine, it is desirable to use straight chain-like ethylamine, propylamine, an octyl amine, a stearyl amine, an oleyl amine, etc. As the addition, extent is illustrated 0.0001 to 0.01% (w/v). Moreover, when inadequate in emulsification, various, still better known emulsification adjuvants can also be used.
[0019] If the cholesterol as a stabilizing agent, phosphatidic acid, etc. can be used as an object for physic, there will be especially no limit. Moreover, as albumin, the thing of the Homo sapiens origin on an antigenic problem is desirable, and can mention a polyvinyl pyrrolidone, polyvinyl alcohol, etc. as a vinyl polymerization object. As a nonionic surfactant, a polyalkylene glycol (-- for example, the average molecular weight 1,000-10,000 -- desirable -- polyethylene-glycol) of 4,000-6,000 -- A polyoxyalkylene copolymer (for example, average molecular weight 1,000-20,000, preferably polyoxyethylene-polyoxypropylene copolymer of 6,000-10,000), a hydrogenated-castor-oil polyoxyalkylene derivative (for example, [the hydrogenated-castor-oil polyoxyethylene-(20)-ether, the **-(40)-ether, the **-(100)-ether], etc.) and a castor oil polyoxyalkylene derivative -- [-- for example The castor oil polyoxyethylene-(20)-ether, the **-(40)-ether, ** -(100)-], such as the ether, etc. can be used.
[0020] The lipid microsphere in this invention is manufactured by the following approach. Namely, in addition to this, the oil component (MCT) of the specified quantity, an emulsifier (preferably phospholipid), the aforementioned additive, etc. are mixed. By heating and homogenizing using a solution and the homogenizers (for example, a high-pressure injection mold homogenizer, an ultrasonic homogenizer, etc.) of nothing and daily use Water-in-oil type dispersion liquid can be made, the water which, subsequently to this, contains the isotonizing agent of an initial complement, a stabilizing agent, etc. can be added, and it can manufacture by homogenizing with said homogenizer again and changing into an oil-in-water emulsion. Depending on the convenience on manufacture, additives, such as a stabilizing agent and an isotonizing agent, may be added after generation of lipid microsphere (refer to JP,58-222014,A).
[0021] Thus, the manufactured lipid microsphere is very detailed and the mean particle diameter of a fat particle is about 0.05-0.5. It is mum and the preservation stability is very good.
[0022] In the above-mentioned lipid microsphere, long-chain-fatty-acid triglyceride (henceforth "LCT") may contain, and it is illustrated as what has suitable fatty-acid triglyceride which uses the fatty acid of the saturation of carbon numbers 16-18, or partial saturation as a configuration fatty acid. LCT may use it as the thing (for example, cotton seed oil, soybean oil, corn oil, peanut oil, safflower oil, etc.) which uses the LCT concerned as a principal component and contains it, for example, vegetable oil which contains 99% or more for the LCT concerned preferably more than 95% (weight). Soybean oil is mentioned as desirable LCT. As soybean oil, the purification soybean oil of a high grade is used suitably, and the purification soybean oil (purity: contain 99.9% or more as triglyceride) of the high grade which refined purification soybean oil further for example, by the steam distillation method, and obtained it more preferably is used. As a fatty acid which constitutes LCT, a palmitic acid, stearin acid, linolic acid, a linolenic acid, oleic acid, etc. are mentioned, for example. the case where LCT is made to contain -- the weight ratio of MCT and LCT -- 4:1-1:4 -- desirable -- 2:1-1:2 -- it is 1:1 still more preferably.
[0023] Since MCT contained in the Alzheimer disease prevention therapy agent of this invention is generally absorbed quickly and easily from an intestinal epithelium cell after administration, is carried by liver through a portal vein, oxidizes by liver and is used as energy, it is used for a nutrient as an energy source whose absorption is an easy high calorie. Therefore, the protein used for the usual nutrient, amino acid, a peptide, the quality of vegetable fat, sugar, minerals, vitamins, other well-known additives (for example, an emulsifier, a stabilizing agent), etc. may be further blended with the Alzheimer disease prevention therapy agent of this invention suitably.
[0024] As protein, vegetable albumen, milk serum protein, and low lactose milk protein are illustrated. As amino acid A valine, a leucine, an isoleucine, a threonine, a lysine, a methionine, a phenylalanine, and a tryptophan are illustrated. As quality of vegetable fat The lipid containing linolic acid, such as safflower oil, corn oil, soybean oil, cotton seed oil, sunflower oil, and linseed oil, and a linolenic acid is illustrated. As sugar Monosaccharides, such as a glucose, a mannose, a galactose, and a fructose, Polysaccharide, such as disaccharides, such as a lactose, cane sugar, and a maltose, a dextrin, and

pregelatinization starch, is illustrated. As minerals Sodium, a potassium, calcium, magnesium, iron, zinc, chlorine, Lynn, copper, manganese, cobalt, molybdenum, chromium, a selenium, etc. are illustrated. As vitamins vitamin A (A1, A2, retinene, provitamin A) and vitamin B1 (a thiamine, aneurine) vitamin B2 (a riboflavin, lactoflavin) Vitamin B6 (a pyridoxine, pyridoxal, pyridoxamine, pyridoxal phosphate) Pantothenic acid, nicotinamide, a biotin, a folic acid, vitamin B12, vitamin C, vitamin D (D2, D3, provitamin D), vitamin E (tocopherol), a vitamin K (K1, K2, and K3), etc. are illustrated.

[0025] In internal use, the Alzheimer disease prevention therapy agent of this invention will be 100g-300g (for example, 10%, if it is a w/v solution) as an amount of adult criteria on the 1st. 1,000 ml - 3,000 ml is prescribed for the patient in several steps. In the case of parenteral administration, as a solution of w/v w/v - 30% 10% In the administration rate 100 - 150 ml/time amount, continuously, in several steps per, a medicine is intubation-impregnation-prescribed for the patient, or it is administered intravenously to the stomach, the duodenum, or jejunum day. In addition, according to age, a symptom, weight, etc., a dose, administration concentration, and an administration rate are fluctuated suitably.

[0026]

[Function] If the Alzheimer disease prevention therapy agent concerning this invention is followed, since MCT which uses the fatty acid of carbon numbers 8-10 as a configuration fatty acid contains as a principal component, the configuration free fatty acid of MCT passes the blood brain barrier, and shifts to cerebrospinal fluid, even acetyl CoA is metabolized in a brain cell, and acetyl CoA for an excess generates acetylcholine with a choline.

[0027]

[Example] Although an example and the example of an experiment are given to below in order to explain this invention to a detail more, this invention is not limited at all by these.

[0028] [Raw material]

A caprylic acid is [the capric acid of MCT;MCT] 23% of medium-chain-fatty-acid triglyceride which came out comparatively and carried out esterification association with the glycerol at random 77%. It is a liquid with transparent colorlessness - fine yellow. The solubility to water is [-14 degrees C and the heating value of 60 mg/dl and the congealing point] 8.3 kcal/g.

[0029] Rough emulsification was performed using the homomixer, having taken the distilled water for injection of 50g (LCT) of example 1 purification soybean oil, MCT50g, Japanese pharmacopoeia glycerol 22.1g, and optimum dose, having mixed 12g of yolk phospholipid as an emulsifier, and having used the whole quantity as 1l. Furthermore, a MANTON-GAURIN mold homogenizer is used and they are total pressure 200 - 250 kg/cm2. It emulsified for 10 minutes under pressurization. The very detailed LCT/MCT emulsion (pH6.3) homogenized by this was obtained. The mean particle diameter of this emulsion is 0.2-0.4. It was mum. After putting this LCT/MCT emulsion into the carboy of suitable quality, it heat-sterilized with the conventional method and the milk-like Alzheimer disease prevention therapy agent for intravenous injection was obtained.

[0030] In example 2 example 1, the MCT emulsion (pH6.3) was obtained according to the example 1 except 100 g Having used MCT, without using purification soybean oil (LCT). The mean particle diameter of this emulsion is 0.2-0.4. It was mum. After putting this MCT emulsion into the carboy of suitable quality, it heat-sterilized with the conventional method and the milk-like Alzheimer disease prevention therapy agent for intravenous injection was obtained.

[0031] Rough emulsification was performed using the homomixer, having taken 50g (LCT) of example 3 purification soybean oil, MCT50g, Japanese pharmacopoeia glycerol 22.1g, 50g of cane sugars, little perfume, and the distilled water for injection of optimum dose, having mixed 12g of yolk phospholipid as an emulsifier, and having used the whole quantity as 1l. Hereafter, it emulsified like the example 1. The very detailed LCT/MCT emulsion (pH6.3) homogenized by this was obtained. The mean particle diameter of this emulsion is 0.2-0.4. It was mum. After putting this LCT/MCT emulsion into the carboy of suitable quality, it heat-sterilized with the conventional method and the milk-like Alzheimer disease prevention therapy agent for intravenous injection was obtained.

[0032] 19.7g of example 4 acid casein is dissolved in the water solution of a suitable quantity of a

sodium carbonate, or potassium carbonate, and after adding MCT12g and 3g of safflower oil in this water solution and homogenizing in it, it was made to dry with spray drying or freeze drying. Next, DL-methionine 0.3 g, dextrin 64g, 1g of vitamins, and 5g of minerals were mixed with V blender, and the powder-like Alzheimer disease prevention therapy agent for taking orally was obtained.
[0033] Example 5MCT5.4 g, safflower oil 1.3 g, 8.87g [of casein hydrolysate], and DL-methionine 0.14g, dextrin 28.8g, Japanese pharmacopoeia glycerol 0.2 g, 1g of vitamins, 5g of minerals, and yolk phospholipid 0.2 g were added to purified water 100 ml, it mixed with the homogeneity machine, and the liquefied Alzheimer disease prevention therapy agent for intubations was obtained.
[0034] Mixed example 6MCT12g, 3g of safflower oil, 19.7g of acid casein, DL-methionine 0.3 g, alpha-corn-starch 54g, 10g of cane sugars, 1g of vitamins, and 5g of minerals to homogeneity, it was made to solidify in the making machine or extruder in which humidification and warming are possible, and the solid Alzheimer disease prevention therapy agent for taking orally was obtained.
[0035] The MCT emulsion containing example of experiment 1MCT10% and yolk phospholipid 1.8 % **** glycerol 2.21% was prepared, it administered intravenously to the rat, and the acetylcholine in a brain homogenate and aging of a choline content were investigated.
[0036] 1. The trial was presented with 80 male rats of 4 weeks old of use animals. In addition, the weights at the time of trial operation were 81.3g-97.3g.
[0037] 2. The administration group configuration, the dose, and the administration rate administration group considered only as the MCT emulsion administration group, and the dose and the administration rate were made into 20 ml/kg and 4 ml/min/animal by which the manifestation of a toxic symptom is checked by administration of a MCT emulsion. The animal used five animals each at the time of 1 inspection.
[0038] 3. Inspection item (1) Decapitation of the rat was carried out in after [administration] 10 minutes, 30 minutes, 1 hour, and the 2nd hour before quantum ** pretreatment administration of acetylcholine, respectively, the brain was extracted immediately, and brain wet weight was measured. Next, it is 500 to brain 100 mg. The 0.2 M perchloric acid (EDTA2Na of 100 muM is included) of mul is added, and it is perchloric acid 500 about a 10-4M ethyl gay choline as an internal standard further. Per [mul / 100] Bottom of ice-cooling 1,000 rpm after mul Adding It homogenized with the Potter mold Teflon homogenizer. Then, in order to perform ** protein completely, centrifugal separation is carried out at 0 degree C after 30-minute neglect into ice for 10,000gx 15 minutes, and it is supernatant liquid 200. It is KHCO3 of 0.2 M to mul. 200 mul In addition, it neutralized. Furthermore, it poured into the high-speed liquid chromatograph which equipped with the electrochemical detector into ice what filtered supernatant liquid with the 0.45-micrometer filter after 30-minute neglect.
[0039] ** Parameter measurement was carried out about acetylcholine and a choline.
[0040] [Test result]
1. Acetylcholine, the acetylcholine in a choline content brain homogenate, and a choline content are shown in the following table 1.
[0041]
[Table 1]

MTC 10% 20㎖/kg 投与後のアセチルコリンおよびコリン含量 (nmole/g) (n=5)

	投与前	投与後10分	投与後30分	投与後1時間	投与後2時間
アセチルコリン	16.8	27.8	29.4	27.0	18.0
	16.4	25.7	28.0	24.0	19.5
	15.6	19.2	28.6	24.1	20.1
	21.7	26.7	27.5	21.5	19.0
	22.3	27.0	29.6	22.6	19.5
平均	18.6	25.3	28.6	23.8	19.2
コリン	120.2	83.5	102.1	106.0	153.4
	118.0	101.7	124.0	110.2	122.0
	111.2	109.4	104.7	106.0	127.4
	132.3	95.8	110.9	115.1	122.9
	121.5	98.3	114.1	112.9	120.0
平均	120.6	97.7	111.2	110.0	129.1

[0042] It increased in the 10th minute after administration, and increased gradually after administration till the 30th minute, and acetylcholine was recovered even to the value before administration after administration in the 2nd hour. On the other hand, although the choline decreased after administration contrary to acetylcholine in the 10th minute, it was recovered after administration in the 30th minute. Change was not accepted in after [administration] 1 hour and, and the 2nd hour as compared with the value before administration.

[0043] Since the octanoic acid whose reason which acetylcholine increases is one of the configuration free fatty acid of MCT shifts to cerebrospinal fluid, an octanoic acid is metabolized by acetyl CoA within a brain cell, and acetyl CoA for an excess is considered to be compounded by acetylcholine with a choline.

[0044] Therefore, like the drugs for the conventional Alzheimer disease, it differs fundamentally, and the action mechanism makes acetyl CoA which should also be called raw material of acetylcholine increase, and generates acetylcholine within a brain, and the Alzheimer disease prevention therapy agent concerning this invention of what is depended on stimulating a receptor with the agonist of a muscarine nature acetylcholine receptor by stimulating composition of acetylcholine is useful as prevention and/or the therapy agent of an Alzheimer disease.

[0045]

[Effect of the Invention] Since acetylcholine is generated by Homo sapiens etc. in a brain cell taking orally or by carrying out parenteral administration, this agent can be used in order to make an Alzheimer disease patient's symptom that the fall of the acetylcholine content within a brain is accepted in the Alzheimer disease prevention therapy agent concerning this invention improve and to prevent an Alzheimer disease.

[Translation done.]

[Claim(s)]
[Claim 1] The Alzheimer disease prevention therapy agent which uses as a principal component the medium-chain-fatty-acid triglyceride whose configuration fatty acid is a fatty acid of carbon numbers 8-10.